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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,405	10/28/2003	Johanna Bentz	3139-6328.1US (ARC 3277 U	7380

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,405	BENTZ ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 10/30/06 to claims 10-12, 14-16, 18-29, 33, and 34 have been entered. Claims 1-35 remain pending in the current application.

Election/Restrictions

Applicant's election without traverse of various species, including "trehalose" as the stabilizing agent; "pituitary adenylate cyclase polypeptide (PACAP)" as the polypeptide; and "amino acid buffers" as the buffers in the reply filed on 10/30/06 is acknowledged. However, after further consideration, the requirement for an election of a single stabilizing agent has been withdrawn.

Examination on the merits will commence at this time on claims 1-35, to the extent they read on the elected species where applicable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8-12, 17, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Carpenter et al. (1989, U.S. Patent 4,806,343; reference A). The claims are interpreted as being drawn to a composition comprising particles that comprise a polypeptide and a stabilizing agent that is a sugar with particular properties, the particles yielding an acidic pH when reconstituted. In some dependent claims, the sugar

is a disaccharide, in particular trehalose. In some dependent claims, the composition comprises a metal ion, in particular a metal ion derived from one of a list of metal ion salts, in an amount present in a particular ratio to the amount of polypeptide. Some claims are drawn to a composition comprising particles that comprise a polypeptide and a stabilizing agent that is a sugar with particular properties and another stabilizing agent, the particles yielding a near-neutral pH when reconstituted. Some claims are drawn to a composition comprising particles that comprise a polypeptide, the particles yielding an acidic pH when reconstituted.

Carpenter et al. teach a composition comprising phosphofructokinase (PFK), a polypeptide; trehalose; and zinc ions, said composition being lyophilized to form a powder that stabilizes the activity of PFK (Example VII; column 6, lines 30-47). Specifically, the composition of Carpenter et al. comprises an aqueous solution of 0.025mg/mL PFK, 0.32mM $ZnSO_4$ (0.051mg/mL), and 60mM trehalose (20.5mg/mL). Therefore, the weight ratio of metal ion to polypeptide is 2.04:1, which is "about" 1:1, "about" 2:1, and "about" 4:1. The zinc ion in the composition of Carpenter et al. is "derived" from $ZnCl_2$ (as in claim 9) in that zinc chloride ionizes in water to yield zinc ion; the claim does not require that the recited divalent salts *per se* be present in the composition.

Carpenter et al. do not explicitly teach that the composition of Example VII provides an acidic or near-neutral pH when reconstituted in any solvent. However, M.P.E.P. § 2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or

substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Since the composition of Carpenter et al. is identical to the compositions as claimed, the compositions inherently have the same physical properties, absent a substantive evidentiary showing to the contrary.

Claims 1-4, 17, 20, 22, 24, 26, and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Andya et al. (2001, U.S. Patent 6,267,958; IDS). The claims are interpreted as being drawn to a composition comprising particles that comprise a polypeptide and a stabilizing agent that is a sugar with particular properties, the particles yielding an acidic pH when reconstituted. In some dependent claims, the sugar is a disaccharide, in particular trehalose. Some claims are drawn to a composition comprising particles that comprise a polypeptide and a stabilizing agent that is a sugar with particular properties and another stabilizing agent, the particles yielding a near-neutral pH when reconstituted. In some dependent claims, the composition further comprises an amino acid buffer or surfactant. Some claims are drawn to a composition

comprising particles that comprise a polypeptide, the particles yielding an acidic pH when reconstituted.

Andya et al. teach compositions comprising HER2 antibody, a polypeptide; trehalose, a sugar; TWEEN 20, a surfactant; and in some cases, histidine, an amino acid buffer, said composition being lyophilized to form a powder that stabilizes the activity of HER2 antibody (column 2, lines 4-41; Table 2, lines 7-14). Specifically, the compositions of Andya et al. comprise 21mg/mL HER2 antibody, 250mM trehalose (86mg/mL), 0.01% or 0.2% TWEEN 20 (10 or 200mg/mL), and 10mM histidine (1.55mg/mL).

Andya et al. do not explicitly teach that the compositions in Table 2 provide an acidic or near-neutral pH when reconstituted in any solvent. However, M.P.E.P. § 2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Since the compositions of Andya et al. are identical to the

compositions as claimed, the compositions inherently have the same physical properties, absent a substantive evidentiary showing to the contrary.

Claims 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Thomson (1989, U.S. Patent 4,816,440; reference B). The claims are interpreted as being drawn to a composition comprising particles that comprise a polypeptide, the particles yielding an acidic pH when reconstituted.

Thomson teaches a composition comprising lyophilized interleukin-2, which is stable (column 9, lines 37-45).

Thomson does not explicitly teach that the composition provide an acidic when reconstituted in any solvent. However, M.P.E.P. § 2112 recites, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established." *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). Since the composition of Thomson is identical to the compositions as claimed,

the compositions inherently have the same physical properties, absent a substantive evidentiary showing to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12, 17, 20-26, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al. taken in view of Andya et al. The claims are interpreted as being drawn to compositions as described above. In some dependent claims, the ratio of the amount of disaccharides to the amount of polypeptide is particularly pointed out.

The teachings of Carpenter et al. are relied upon as above. Carpenter et al. do not exemplify the ratios of trehalose to PFK recited in claims 5-7. Carpenter et al. do not exemplify a lyophilized composition comprising each and every metal ion recited in claim 9.

Andya et al. teach compositions for stabilizing any of a wide variety of proteins (Abstract; column 1, line 62, through column 2, line 19; column 14, line 57, through column 16, line 67). Andya et al. further teach that lyoprotectants, compounds that protect proteins during lyophilization and storage, include sugars such as sucrose and trehalose; amino acid buffers such as monosodium glutamate and histidine; and salts such as magnesium sulfate (column 9, lines 21-33); lyoprotectants may be added as necessary (column 9, lines 34-38). The composition of Andya et al. may further comprise a surfactant (column 2, line 63, through column 3, line 3). Andya et al. teach that the ratio of lyoprotectant to protein may be modified as necessary (column 2, lines 47-56).

A person of ordinary skill in the art would have had a reasonable expectation of success in including an amino acid buffer and/or a surfactant in the composition of Carpenter et al. because Andya et al. teach that amino acid buffers and surfactants may be included in lyophilized compositions comprising any of numerous diverse proteins. The skilled artisan would have been motivated to include amino acid buffers and/or surfactants because Andya et al. teach that these molecules protect the protein during the lyophilization and storage processes.

The selection of the amount of trehalose, metal ion, amino acid buffer, and/or surfactant to add to the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carpenter et al. teach that the amount may be modified as necessary (column 3, lines 19-35). Furthermore, Andya et al. broadly teaches that proteins may be lyophilized with varying amounts of trehalose as necessary. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the metal ion to include the composition of Carpenter et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Carpenter et al. teach that the addition of calcium, magnesium, or zinc increases the activity of PFK in the composition compared to compositions lacking such metal ions (Example III; Table I; column 5, lines 5-31). A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include amino acid buffers and/or surfactants in the composition of Carpenter et al. because Andya et al. teach that, like trehalose and metal ions, amino acid buffers and surfactants are lyoprotectants. It is well established that duplicating components with similar functions within a composition is obvious; see *In re Harza*, 274 F.2d 669, 124 USPQ 378 (CCPA 1960) and M.P.E.P. § 2144.04. It would have been further obvious to modify the amount of trehalose, metal ion, amino acid buffer, and/or surfactant and the character of the metal ion included in the

composition of Carpenter et al. because Carpenter et al. and Andya et al. suggest such optimization.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1-12, 17, 20-28, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al. and Andya et al. as applied to claims 1-12, 17, 20-26, and 30-32 above, and further in view of Thomson. The claims are drawn to compositions as described above. In some dependent claims, the surfactant is sodium dodecyl sulfate (SDS).

The teachings of Carpenter et al. and Andya et al. are relied upon as above. Carpenter et al. and Andya et al. do not teach a composition in which the surfactant is SDS.

Thomson teaches a lyophilized composition comprising interleukin-2 or interferon-beta and SDS (column 3, lines 30-39).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the SDS of Thomson for the surfactants of Andya et al. because Thomson teaches that SDS, like the surfactants of Andya et al., protect proteins from lyophilization. The skilled artisan would have been motivated to make this modification because Thomson teaches that SDS maintains the stability of lyophilized proteins.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the SDS of Thomson for the surfactants of

Andya et al. because the two are functional equivalents, *i.e.* they protect proteins in lyophilized compositions. Therefore, these may be considered to be art-accepted equivalents.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Claims 1-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carpenter et al., Andya et al., and Thomson as applied to claims 1-12, 17, 20-28, and 30-32 above, and further in view of Nishimura et al. (1999, U.S. Patent 5,861,284; reference C) and Arimura et al. (1992, U.S. Patent 5,128,242; reference D). The claims are drawn to compositions as described above. In some dependent claims, the polypeptide is a pituitary adenylate cyclase polypeptide (PACAP).

The teachings of Carpenter et al., Andya et al., and Thomson are relied upon as discussed above. Carpenter et al., Andya et al., and Thomson do not teach a composition in which the polypeptide is PACAP.

Nishimura et al. teach a composition for stabilizing polypeptides with an amide at their C-terminal or a disulfide linkage in the molecule, one of which is PACAP (column 4, lines 39-56, particularly lines 51-52). The composition of Nishimura et al. is lyophilized, *i.e.* it is a powder comprising particles (column 12, lines 53-63) and may further comprise trehalose (column 12, lines 23-26) as well as buffers, salts, and/or surfactants (column 12, lines 49-53).

Arimura et al. teach that PACAP and fragments thereof have therapeutic activity, for example in stimulating the pituitary (column 6, section 5.3 starting at line 45).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the PACAP of Nishimura et al. for the PFK of Carpenter et al. because Nishimura et al. teach that PACAP, like PFK, can be stably stored by lyophilizing a solution of the protein, trehalose, and salts; furthermore, Andya et al. teach that a diverse group of proteins can be preserved in such a compostion. The skilled artisan would have been motivated to make this substitution in order to preserve active PACAP, which Arimura et al. teach is a therapeutic protein for pituitary disorders, until it is needed to treat a patient.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute the PACAP of Nishimura et al. for the PFK in the composition of Carpenter et al. because Arimura et al. teach that PACAP is a valuable therapeutic biomolecule, and because Nishimura et al. teach that PACAP can be preserved in a composition similar to that of Carpenter et al.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

No claims are allowed. No claims are free of the art.

Applicant should specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is

noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart